GR

ORIGINAL SUBMISSION

000002

ENVIRON

May 2, 2001

Dr. Linda Kahl
Office of Premarket Approval, HFS-200
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW
Washington, DC 20204

Dear Dr. Kahl:

We wish to notify you that DMV International has determined that bovine lactoferrin is "generally recognized as safe" (GRAS") for use as an ingredient in sports and functional foods. Accordingly, bovine lactoferrin is exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act. We are hereby submitting the attached document, relied upon by DMV International, to make its GRAS determination, for the use of bovine lactoferrin in sports and functional foods.

A GRAS Notification for bovine lactoferrin was submitted to FDA as GRN 000042, with letters submitted to this file on September 11, 2000, January 12, 2001 and January 15, 2001. In a letter of March 26, 2001, from FDA to ENVIRON Corp and DMV International, FDA indicated that the submissions to date for GRN 000042 were silent with regard to the potential for allergenicity or autoimmune problems from ingestion of milk-derived lactoferrin at the intended levels of exposure. FDA requested a description of the basis to conclude that experts had considered these issues and would agree that the potential for allergenicity or autoimmune problems does not raise a safety concern.

In response to FDA's recommendations outlined in the letters of March 26, 2001 and April 23, 2001, we are hereby submitting the attached document, which provides the conclusions of an expert panel convened to address the issues discussed above, of potential for allergenicity or autoimmune problems. The panel identified the cited references from the publicly available literature as being the most relevant to address the issues of allergenicity and autoimmune problems from ingestion of bovine lactoferrin. These papers were considered as the basis for their expert opinion on these matters. As requested by FDA in a phone message to Dr. Claire Kruger of April 30, from Dr. Paulette Gaynor, hard copies of these references are included in the submission.

DMV International also requests that FDA incorporate, in this submission, the information submitted under GRN 000042.

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[redacted]

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Any additional data and information that serve as the basis for this GRAS notification will be sent to FDA upon request or are available for the FDA's review and copying at reasonable times at the office of Claire Kruger, Ph.D., Principal, ENVIRON Corporation, 4350 North Fairfax Drive, Suite 300, Arlington, VA. 22203, telephone (703)516-2309, facsimile: (703)516-2393.

Sincerely,

Claire L. Kruger, Ph.D. D.A.B.T.
Principal

cc: V. Frankos
R. Nimmagudda
S. Taylor
L. Rosenwasser
B. Lonnerdal
J. Brock
S. Sicherer
H. Sampson

Expert Panel Conclusions

The undersigned group of scientific experts is qualified by training and experience to judge the allergic and immunologic issues related to the ingredient uses of bovine lactoferrin in the diet. This Panel agrees that the increased consumer exposure to bovine lactoferrin arising from the uses of DMV bovine lactoferrin in products intended primarily for adults and at the levels of exposure specified in GRN 000042, would be highly unlikely to induce allergy or autoimmune disease.

It is acknowledged that bovine lactoferrin may be a minor cows' milk allergen. Although scientific information exists to suggest that bovine lactoferrin can induce IgE antibodies in the Brown Norway rat model, this model is not an adequate, appropriate or validated model for prediction of allergic disease in humans. Some milk-allergic infants are known to be sensitized to bovine lactoferrin. However, the likelihood that several-fold increases in background exposure to bovine lactoferrin in older children and adults would result in allergic sensitization is remote given the large existing background level of exposure. Furthermore, allergic sensitization to milk is a decidedly rare event in older children and adults. A margin of safety exists between the current EDI and the level at which concerns would arise for an increased risk of allergic sensitization. This is particularly true in light of the exaggeration of exposure to other dietary proteins, including other allergenic milk proteins that have been introduced into the diet at levels of exposure that are an order of magnitude above the EDI for DMV bovine lactoferrin. However, food products containing bovine lactoferrin should be clearly labeled as containing a milk protein so that existing milk-allergic consumers can avoid these products.

The likelihood of increased consumer exposure to bovine lactoferrin causing or exacerbating autoimmune disease is considered remote. Available literature suggests that the proposed exposure level is at least an order of magnitude below that shown to cause a systemic immune response to orally-administered lactoferrin. Even if such a response were to occur, there is no evidence that it could lead to an autoimmune response to human lactoferrin. Finally, although there is an extensive literature documenting the presence of anti-lactoferrin autoantibodies in various autoimmune diseases, there is no evidence that these antibodies play any role in the pathology of these diseases. Thus development of a harmful autoimmune response as a result of the ingredient use of lactoferrin would require a combination of circumstances, each of which is considered unlikely to occur.

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Date: 4-25-01

The conclusion of this panel is that bovine lactoferrin, at the proposed levels and for the uses specified by DMV International, is safe and GRAS. The expert panel participants were:

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GENERALLY RECOGNIZED AS SAFE DETERMINATION FOR BOVINE LACTOFERRIN

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Prepared for

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Fraser, NY

Prepared by

Environ International Corp.
Arlington, Virginia

May 2, 2001

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Meredith C, Atkinson HAC. 2001. Development of methods to predict the allergenic potential of food proteins. *Report to U.K. Food standards Agency.*

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Development of methods to predict the allergenic potential of food proteins

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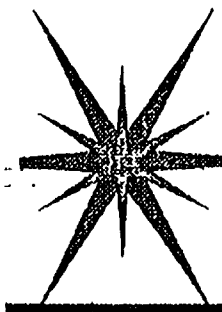


Introduction

- Rapid changes have occurred in methods of food production and processing which cover a wide variety of products. Concerns have been expressed relating to the possible allergenicity of novel proteins or those produced using new technologies that will be introduced in to the diet. Whilst techniques exist for establishing the cross-reactivity of novel proteins with IgE in serum banks, this approach simply predicts whether there is a potential to elicit an allergic response in a previously sensitised individual. This strategy cannot predict the potential of a food protein to induce sensitisation. In order to predict the allergenicity of newly introduced proteins in the diet it is necessary to use an animal model. It is therefore first necessary to have information on the performance of dietary proteins with known allergenic potential within the chosen animal model.
- We are developing a battery of tests which can be used to predict the allergenic potential of these novel food products and to derive risk factors. We are using the Brown Norway (BN) rat model to evaluate the allergenic potential of a range of known food allergens. We report here the results of a series of experiments designed to rank food proteins in terms of their "inherent allergenicity" (induction of IgE), resistance to digestion and capacity to sensitise by the oral route. Subsequently, we would consider the placement of novel proteins which may be introduced in to the diet within this allergenicity ranking.

HAC 2000

Methods 1

- Ovalbumin, grade VII (OA VII) and grade II (OA II), lactoferrin (LF), bovine serum albumin (BSA) and carrageenan Type V (CGN) were obtained from Sigma Ltd (Poole, Dorset UK).
- Brown Norway (BN) rats (male 6-8 weeks old) were used for immunisation procedures, while Sprague-Dawley (SD) rats (250-400 g) were used for the analysis of reaginic antibody (Atkinson & Miller 1994). Both strains of rat were obtained from Harlan UK. Ltd (Bicester, Oxon, UK). Animals received a nutritionally adequate diet, either Teklad 9608 rat and mouse diet (ovalbumin- and milk-free), supplied by Harlan UK Ltd for BN rats, or Rat and Mouse No 1 expanded, supplied by Special Services Ltd (Witham, Essex, UK) for SD rats. Both food and water were freely available. They were acclimatised for a minimum of 6 days before use.
- The presence of reaginic antibody was assessed by passive cutaneous anaphylaxis (PCA)(Ovary 1964). The diameter of dye extravasation at the site of serum injection was measured and the area of dye extravasation (ADE mm^2) calculated. The class of reaginic antibody was confirmed as IgE by Western blotting using peroxidase labelled mouse anti-rat IgE (MARE 1).

H.A.C. 2000

Methods 2

- Resistance to *in vitro* peptic digestion was assessed at intervals between 0 to 60 minutes incubation. SDS-PAGE with Coomassie blue staining was used to determine the presence of the protein.
- For examination of inherent allergenicity groups of eight animals were injected intraperitoneally with either LF, OA II, OA VII or BSA at doses of 0.01, 0.1, 1.0, 10, 100 and 1000 µg, together with 1 mg CGN in 1 ml of saline. On day 28 they were killed by exsanguination under barbiturate anaesthesia. The sera were assessed for the presence of antigen-specific reaginic antibody.
- For examination of the capacity to induce sensitisation by the oral route groups of eight animals were gavaged (0.5ml/100g body weight) twice a week for six weeks with either OA II, LF or BSA in distilled water at dose levels of 0.5, 5.0, 50 and 100 mg/kg. They also received 1 mg CGN in 1 ml of saline once a week for six weeks. Animals were bled at weekly intervals from day 14 onwards and killed by exsanguination under barbiturate anaesthesia on day 42. The sera were assessed for the presence of antigen-specific reaginic antibody.

HAC-2000

Results 1

- All proteins were found to be capable of inducing reaginic antibody production. Western blotting confirmed the class of reaginic antibody was IgE.
- The results have been presented as the mean and SD of the ADE. Based on the number of responders, i.e. those animals with positive PCA responses, dose response curves were constructed.
- It would appear that comparison of the dose level calculated to produce 50% responders (ED50) would be the most effective way of comparing the inherent allergenicity of a range of proteins. Using this approach ED50s of 40-50 ng for LF, 500-600 ng for OA II, 5-6 µg for OAVII and 10 µg for BSA were observed. Hence the comparative allergenic potential of these proteins can be ranked LF>OAII>OVA>VII>BSA.
- After 5 minutes incubation with simulated gastric fluid both BSA and LF were digested, whilst OAII and OAVII were still present after 60 minutes incubation as seen by Coomassie stain.

HAC 2000

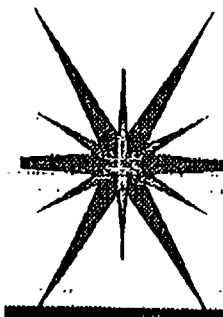
Results 2

- All three proteins examined were capable of inducing reaginic antibody production following oral exposure.
- The kinetics of the oral responses differed in relation to both the protein and the dose level used, for example:
  - Sensitisation with BSA could only be achieved at the highest dose level of 100 mg/kg.
  - The responses at the 0.5 and 5 mg/kg LF dose levels only developed after 42 days.
  - At the OAII 100 mg/kg dose level the maximum number of responders peaked before day 42.
- In order to compare the allergenic potential following oral exposure dose responses were constructed using the maximum number of responders. To take account of the BSA response only at the highest dose level the allergenic activity was compared using an ED75% of responders. The ED75s were found to be 5.0, 50 and 100 mg/kg for OAII, LF and BSA respectively.

Discussion

- The characteristics of an allergen and the factors that influence the development of sensitisation are complex. The induction of oral sensitisation will depend not only upon the inherent allergenicity and stability to digestion of a protein, but also the level and duration of exposure. These aspects are addressed within the approach adopted in these experiments.
- The relationship between the inherent allergenicity and stability of digestion on oral sensitisation is highlighted by LF and OAII. The inherent allergenicity ranked the proteins in the order LF<OAII<BSA, however OAII unlike LF was resistant to proteolytic digestion which was reflected in the ranking OAII<LF<BSA obtained following oral exposure. This ranking probably reflects the human experience.
- The application of the toxicological concept of dose-response to an essentially immunological phenomenon provides useful information on the allergenic potential of a food protein, permits a ranking to be established and may help in the choice of food production and processing strategies
- The BN rat has been shown to be suitable model for investigating both inherent and oral allergenicity . We are currently using this model to investigate the stability of the IgE epitopes on the protein residues following digestion.

RAC 2000



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Acknowledgements

- This work was supported by MAFF UK.

Antigen-specific reaginic antibody responses

Protein		ADE mm² Protein µg 0.01	0.1	1.0	10	100	ED50
BSA	Mean	0	78	138	175	274	
	SD	0.0	0.0	60.1	94.0	91.3	10 µg
	No. Responders	0/8	1/8	4/8	7/8	6/8	
OAVII	Mean	0	0	0	179	295	
	SD	0.0	0.0	0.0	84.4	104.7	5-6 µg
	No. Responders	0/8	0/8	0/8	5/8	4/8	
OAII	Mean	0	0	74	236	287	
	SD	0.0	0.0	46.1	65.5	71.3	500-600 ng
	No. Responders	0/8	0/8	5/8	7/8	8/8	
LF	Mean	0	134	259	199	174	
	SD	0.0	98.3	80.1	31.5	52.9	40-50 ng
	No. Responders	0/8	6/8	7/8	8/8	7/8	

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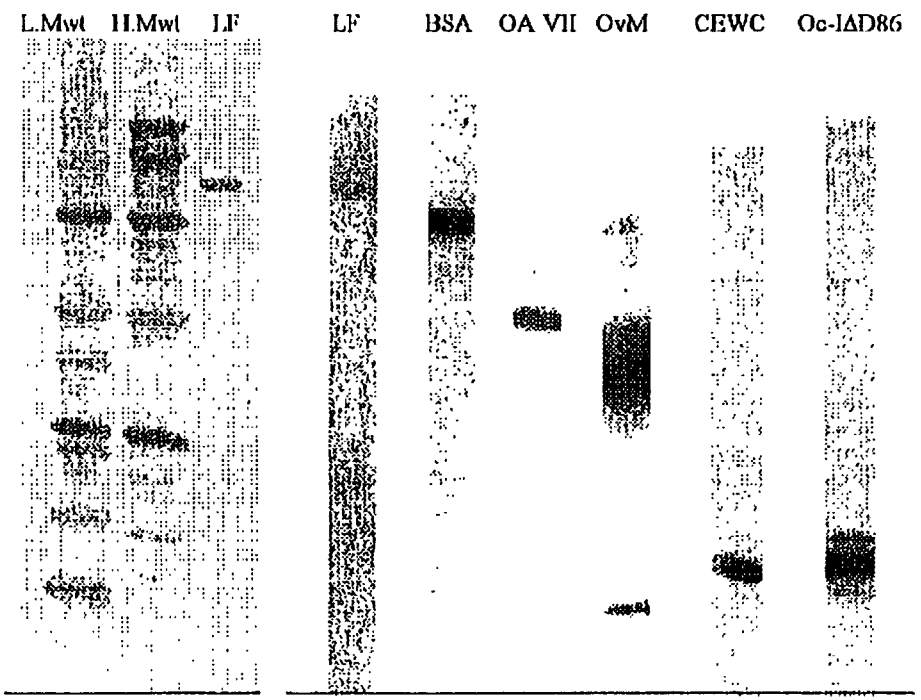
Antign-specific IgE antibody

SDS PAGE gel



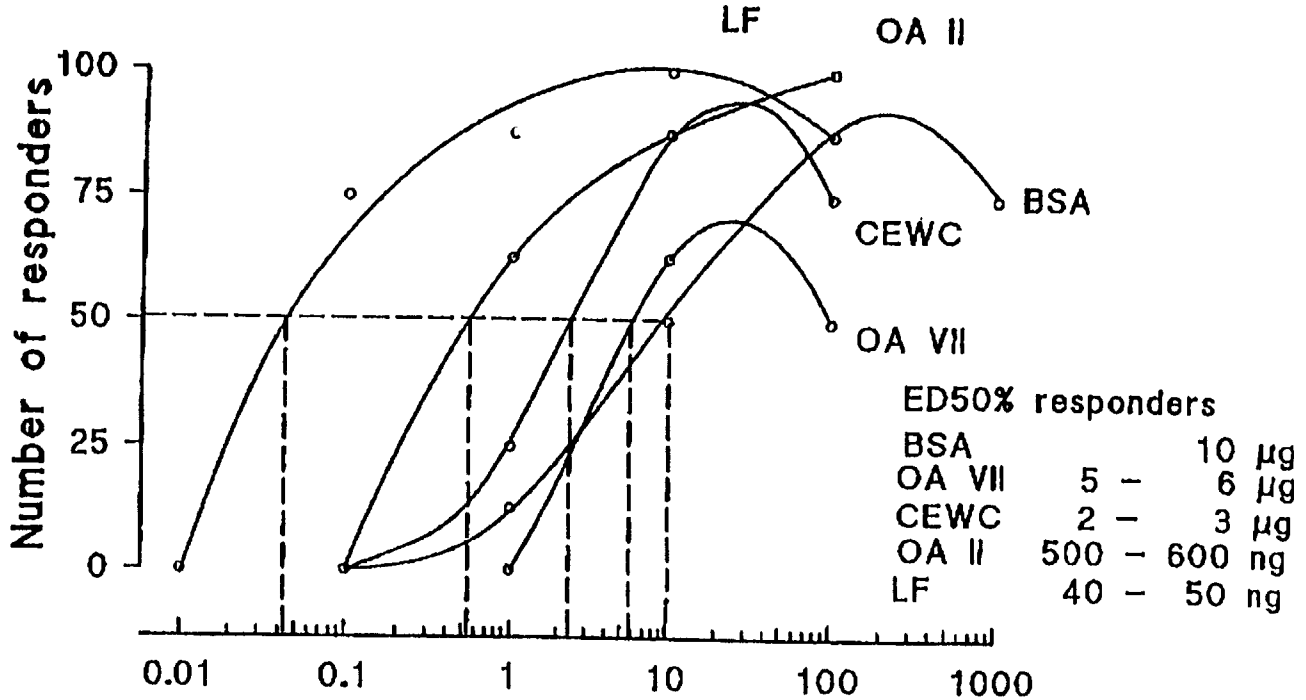
Ponceau stain

Western blot with antigen-specific BN serum

Mouse monoclonal anti-rat IgE peroxidase labelled antibody
Visualised using chemiluminescent system ECL

HAC-2000

Inherent allergenic potential of a range of food proteins



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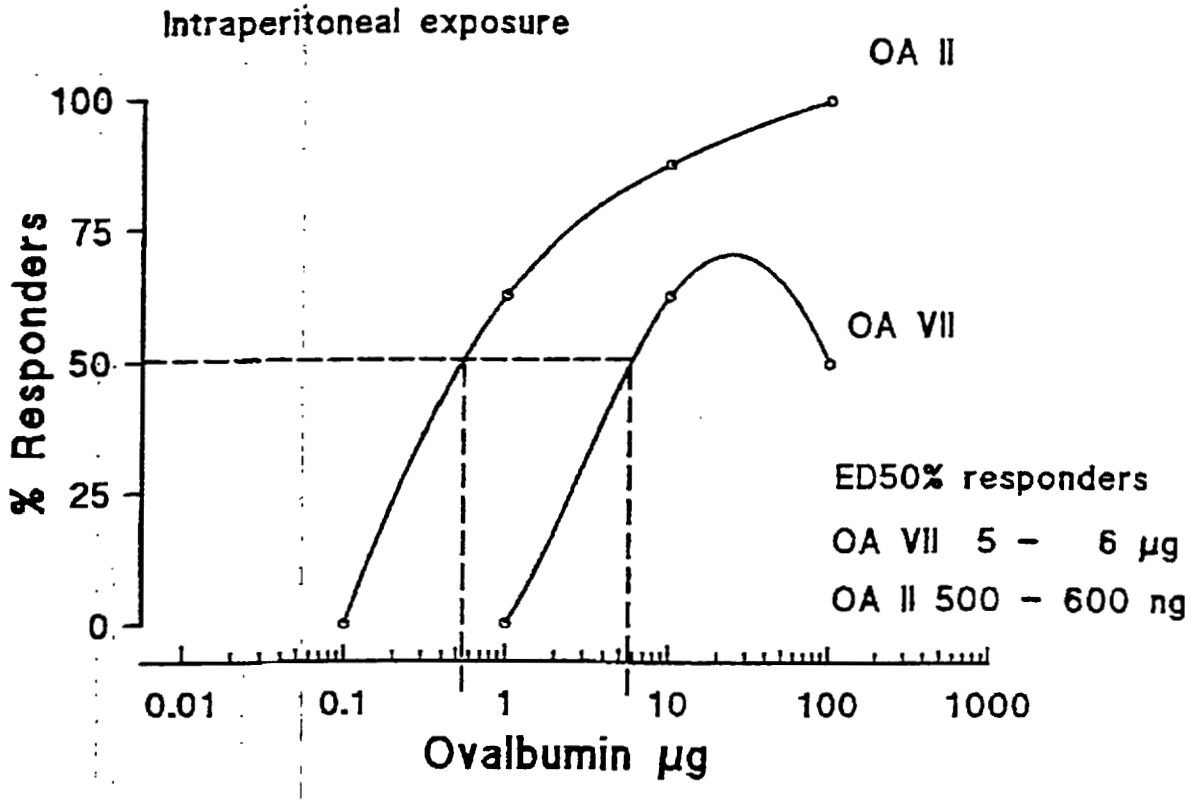
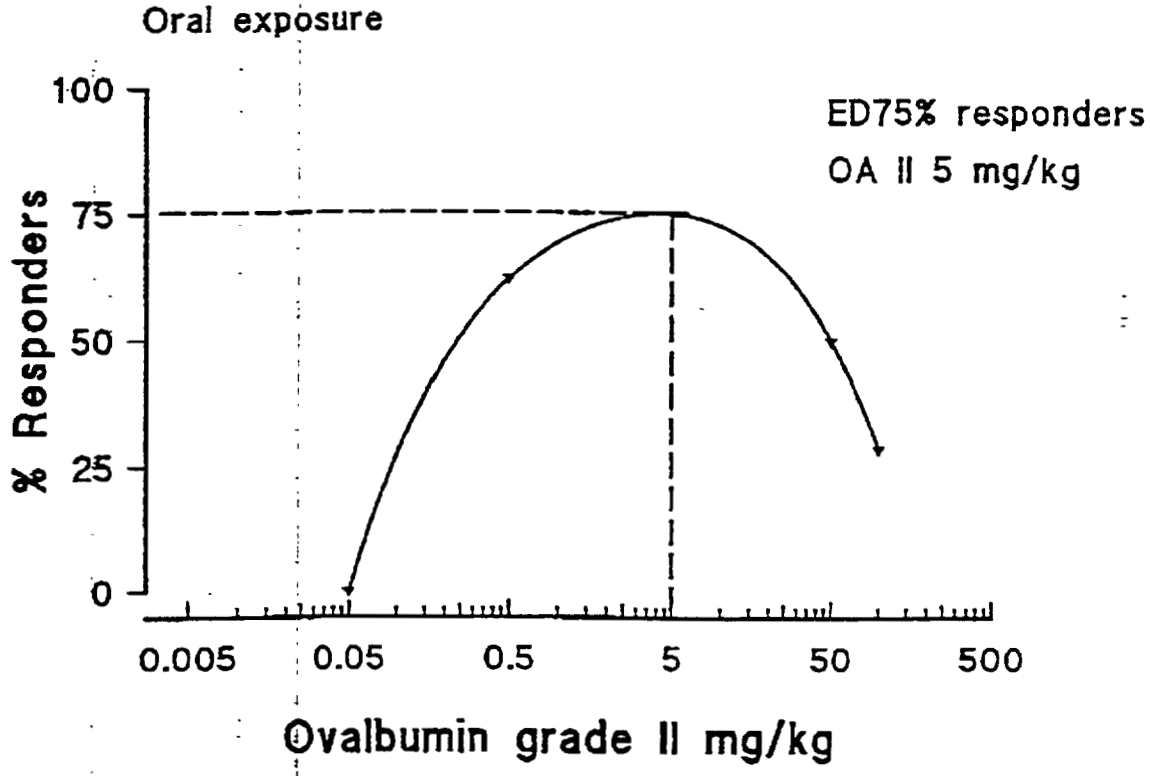
Dose response curves for Ovalbumin





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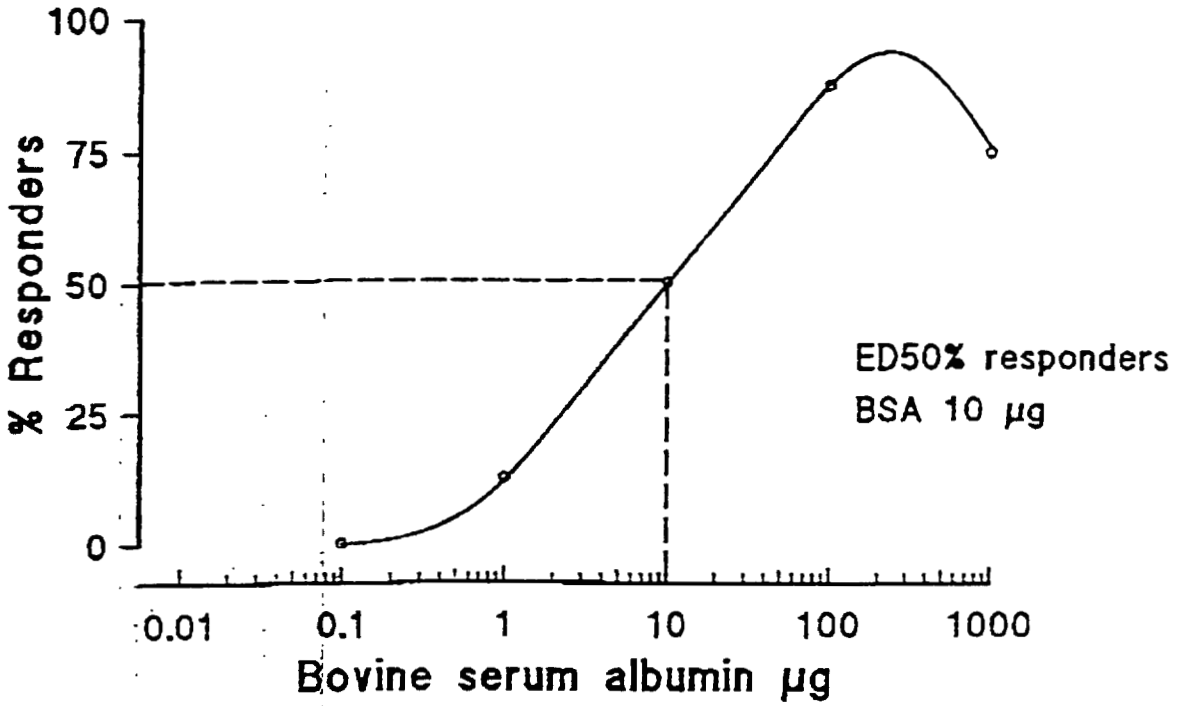
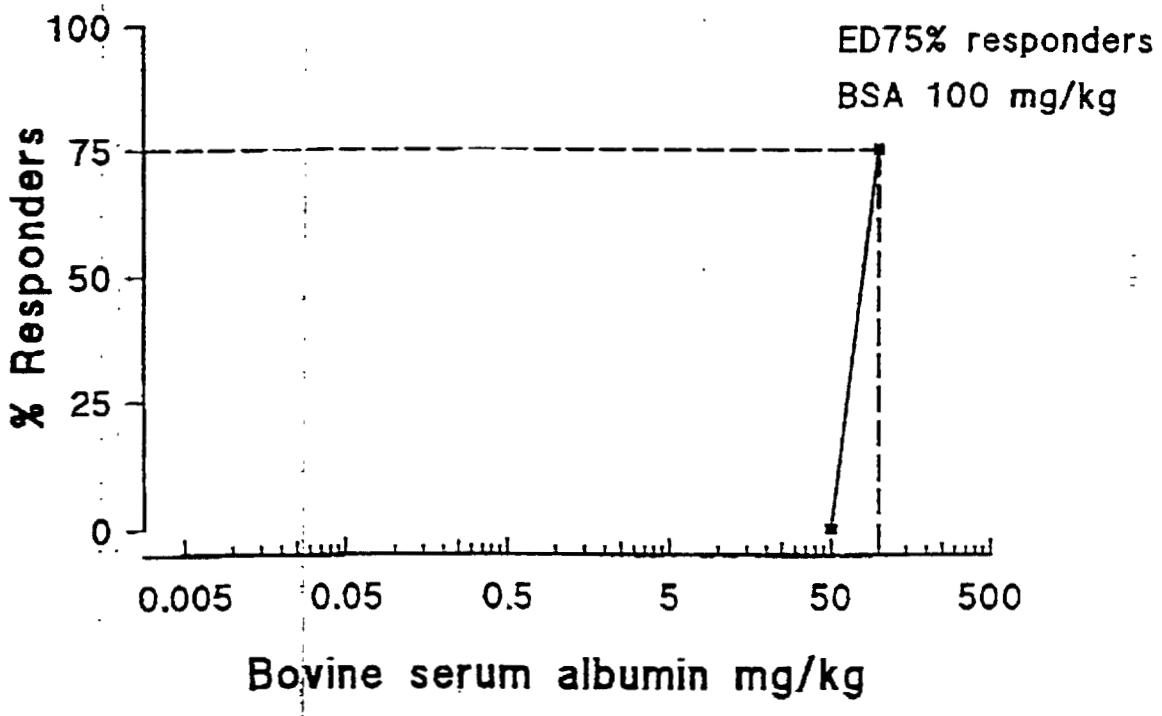
Dose response curves for Bovine serum albumin

Intraperitoneal exposure



Oral exposure



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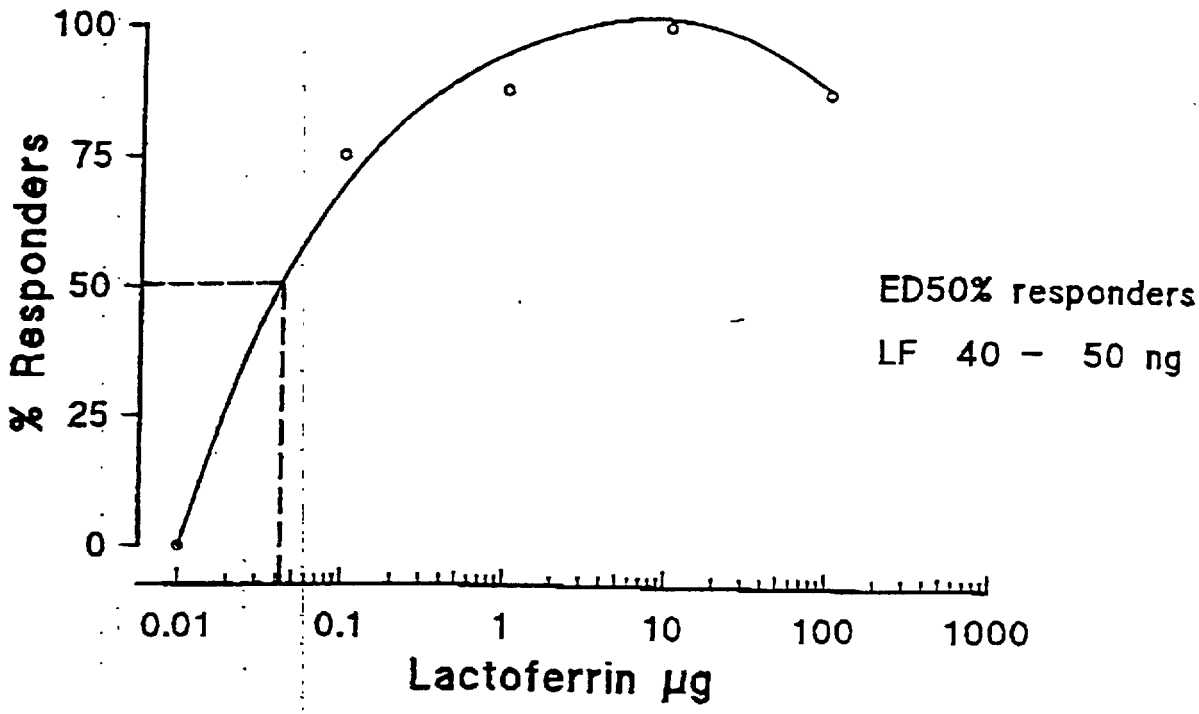
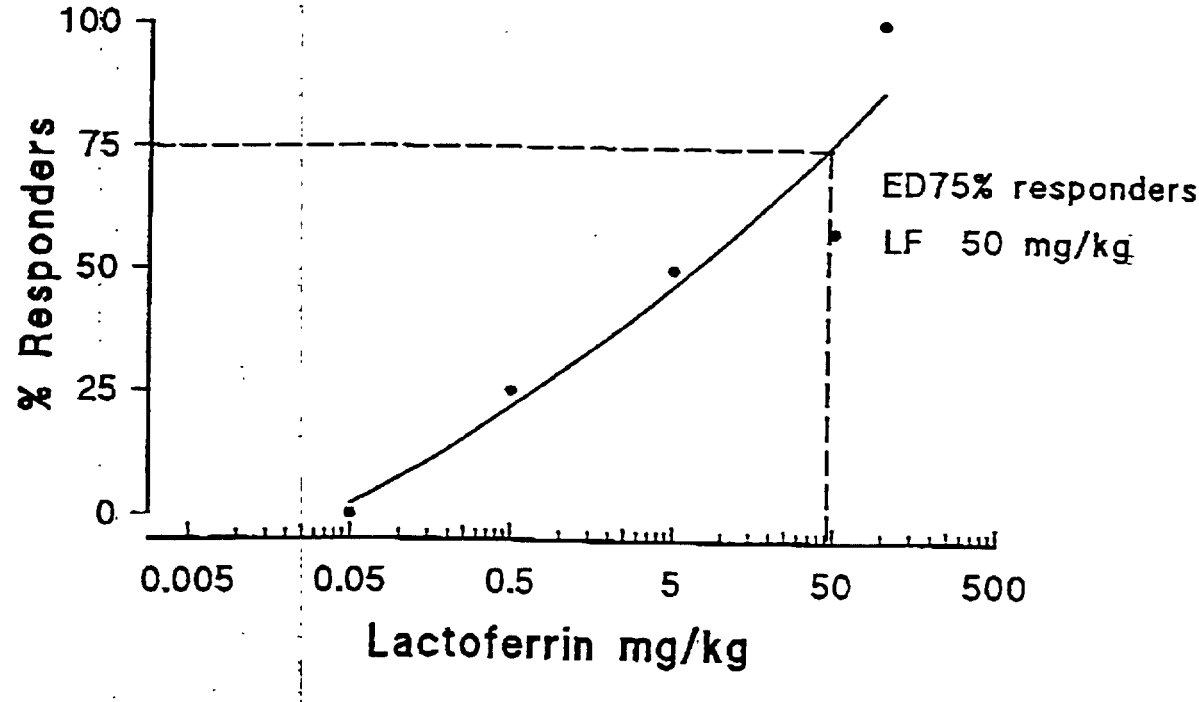
Dose response curves for Lactoferrin

Intraperitoneal exposure



Oral exposure



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